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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,095	KRAUSE ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-13,15-17 and 20-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-13,15-17 and 20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on March 12, 2008.

Currently, claims 10-13, 15-17, and 20-24 are under examination on the merits.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Applicant's arguments filed on March 12, 2008 have been fully considered but they are not persuasive. Applicant's arguments pertain to the newly amended claims. Therefore, applicant's arguments are moot in view of the new ground(s) of rejection. See below for new rejections.

The declaration under 37 CFR 1.132 filed on March 12, 2008 is insufficient to overcome the rejection of claims 10-13, 15-17, and 20-23 based upon the Srisawat et al. reference as set forth in the last Office action for the following reasons:

The declarant states that Srisawat et al. were "never successful at making a construct containing two functional tags", because only one of the tags was functional. Contrary to declarant's statement, Srisawat et al. taught a recombinant construct comprising the S1 streptavidine aptamer and the D8 Sephadex aptamer ("S1- plus D8-tagged RPR1"). They taught

that "Both Sephadex and streptavidin tags enable the specific and rapid isolation of tagged RNase P from crude yeast lysates as shown by Northern blot analyses of RPR1 RNA". See page 160. Thus, examiner does not understand the basis for the declarant's allegation that Srisawat et al. were "never successful at making a construct containing two functional tags".

The declarant further states that "Simply adding short spacers did not work for them". Again, the declarant makes this statement without providing objective evidence that Srisawat et al. indeed attempted to add short spacers and failed to produce a construct containing two functional tags and short spacers. Nowhere in the Srisawat et al. reference is there a statement acknowledging that they actually attempted to insert short spacers and failed to do so.

The declarant further states that the inventors themselves have tried to add short spacers, which "does not work in general" and that "there are many reasons for failure, and very few solutions". Again, applicant's own experience of difficulty with adding spacers does not demonstrate that one of ordinary skill in the art would fail to make the claimed construct. The declarant further alleges that "there are still no other successful RNA multi-tagging systems available". Contrary to declarant's allegation, the Srisawat et al's RNA multi-tagging system is a successful RNA multi-tagging system as detailed above.

The declarant further alleges that the applicants are the first to recognize the advantage of having two or more different tags in one construct. Again, a successful multi-tagging system comprising two different RNA aptamer tags was taught by Srisawat et al. and furthermore, the concept of multi-tagging system for protein isolation and purification was widely known in the art at the time of the invention as evidenced by a number of prior art teachings. See below.

To summarize, the declaration does not provide any factual evidence, and therefore, it is not persuasive to overcome the pending rejections based on the Srisawat et al. reference.

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-13, 15-17, and 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Srisawat et al. (*Methods,* 2002, 26:156-161, citation of record) in view of Puig

et al. (*Methods,* 2001, 24:218-229), Honey et al. (*Nucleic Acids Research,* 2001, 29:e24), Maquat (*Methods,* 2002, 26:93-94), Hermann et al. (*Science,* 2000, 287:820-825), Williams et al. (*Nucleic Acids Research,* 2001, 29:1476-1483).

The claim is drawn to an RNA fusion molecule having a target RNA sequence, a polynucleotide sequence of 4-10 identical nucleotides, and two different RNA tags, wherein the polynucleotide sequence separates the target RNA sequence and the RNA tags, and functions to ensure proper folding of the RNA tags and to discourage interaction between the RNA tags and the target RNA sequence, wherein identical restriction sites flank said polynucleotide sequence.

Srisawat et al. teach a fusion RNA molecule comprising two different RNA tags, S1 and D8. They teach that the RNA tags can be used to rapidly and specifically isolate a particular precursor or product form of RNA of interest from RNPs or characterization of RNPs containing lethal mutations (page 161). They teach that RNA affinity tags (or aptamers) with high affinity to S1 and D8 are designed by using the SELEX method (page 157). They expressly teach that one of main considerations in constructing affinity tag molecules is the folding problem and that the "folding problem is "simply" a matter of inserting the tag in such a way that both the tag and the RNA of interest remain **correctly folded**." (page 158) They teach that one potential solution to the steric blockage problem is to "place a **short spacer** between the tag and the main body of the RNA…A complete folding check is recommended to ensure that the spacer also does not interfere with folding of the tag or the main RNA". See page 159. Srisawat et al. do not teach that the spacer (or insulator) sequence is flanked by identical restriction sites, nor do they teach that the RNA tag interacts with a ligand in a reversible fashion.

Puig et al. teach that they have developed a tandem affinity purification (TAP) method to allow raid purification of protein complexes, wherein the TAP method requires fusion of the TAP tag consisting of two ProtAs and a CBP to the target protein of interest. They teach that because each protein has unique properties, it has been impossible to design a general purification strategy useful for all cases. They, therefore, teach that a generic purification protocol for routine and automated protein complex purification by utilizing the fusion of tags, peptides, or protein domains to protein targets is highly desired in the art for facilitate proteome analysis. They teach that the TAP system utilizes standard DNA cloning procedures such as unique restriction sites in an appropriate expression vector. They inform that there is a consideration to make with regard to tagging: "A problem intrinsic to the TAP strategy and any tagging method is the possibility that a tag added to a protein might not be sufficiently exposed to allow binding of the protein to the affinity beads or might affect protein function." See page 227.

Honey et al. teach a multiple affinity purification tag (MAFT) method comprising three different affinity tags (CBP, HIS6, and HA3) that are inserted between the two identical restriction endonuclease sites, NotI, wherein the tags are inserted by recombination. See page 1 and Figure 1.

Maquat teaches that many investigators in the molecular biology art have developed experimental methods to study RNA-protein interactions. Maquat teaches that fusion RNAs comprising SELEX-generated high-affinity tags (aptamers) are useful to study RNA-protein interactions, upon which new approaches can be developed.

Hermann et al. teach that aptamers are highly specific because of their "folding around the ligand provides numerous discriminatory intermolecular contacts". See page 823. They teach an RNA aptamer binding to MS2 coat protein. See Table 1. They teach that RNA aptamers contain a critical unpaired adenine nucleotide and looped out in the protein-bound complexes. They teach that "This bulged adenine is one of three unpaired bases that mediate the specific recognition of the RNAs by the MS2 coat protein." See page 823. They further teach that aptamers are superior (higher affinities) and inexpensive substitutes for antibodies comprising polypeptide sequences and therefore provide useful molecular tools in biotechnology. See page 823. They further teach that the aptamer-ligand binding is reversible due to ligand-dependent conformational change of the aptamer domain. See page 823.

Williams et al. teach a 5-nucleotide spacer consisting only of adenines ("AAAAA"). They teach that a polynucleotide comprising four or more consecutive adenines is long enough to fix the DNA in the rigid configuration required. See page 1482.

It would have been obvious to one of ordinary skill in the art to modify the TAP of Puig et al. or the MAFT of Honey et al. by replacing the peptide tags of the TAP or MAFT system with the SELEX-generated RNA aptamer tags of Srisawat et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success, because Srisawat et al. taught that a construct comprising two different RNA aptamer tags successfully and specifically isolate proteins, and because Maquat expressly taught that one of ordinary skill in the art can further modify or improve upon the construct of Srisawat et al. to study RNA-protein interactions. Furthermore, one of ordinary skill in the art would have been motivated to replace the peptide (or protein) tags of the TAP or the MAFT

protein isolation/purification system with the SELEX-generated RNA aptamer tags, because Hermann et al. taught that aptamers are much better than polypeptide-containing antibodies due to their higher affinities and specificities for their ligands. Knowing the superior properties of aptamers compared to polypeptides, one of ordinary skill in the art would have been motivated to replace the TAP tags consisting of two ProtAs and a CBP of Puig et al. or the MAFT tags consisting of CBP, HIS6, and HA3 of Honey et al. with two MS2 coat protein RNA aptamers and one S1 RNA aptamer, because both MS2 coat protein RNA aptamer and the S1 RNA aptamer were known to be useful for specific ligand binding. While constructing the multiple tandem affinity purification/isolation system comprising RNA aptamers as tags, one of ordinary skill in the art would have been motivated to place a short spacer between the RNA aptamer tags and the target RNA sequence because Srisawat et al. explicitly recommended a skilled artisan to ensure whether both the tag and the RNA of interest remain correctly folded and suggested to place a short spacer between the RNA aptamer tags and the target RNA sequence to resolve the folding problem. Moreover, in addition to such teachings of Srisawat et al., Puig et al. also taught that any tagging method involves a potential problem wherein a tag added to a protein might not be sufficiently exposed to allow binding of the protein to the affinity beads or might affect protein function. Therefore, a skilled artisan aware of the precautionary teachings with regard to "tagging" would have been motivated to perform the "complete folding check" as recommended by Srisawat et al. In order to ensure the proper folding of the RNA aptamer tags for their ligand binding as well as the steric hindrance/interference/blockage problem that was well known to be associated with "tagging", one of ordinary skill in the art would have heeded the suggested solution of Srisawat et al. and therefore would have placed a short spacer sequence between the

tags and the target RNA sequence. In so doing, the skilled artisan would have looked into potential spacer nucleotide sequences available and known in the art, such as those of Williams et al. Since Williams et al. taught that a polynucleotide comprising four or more consecutive adenines is able to fix DNA configuration, and since Hermann et al. taught that an unpaired, bulged adenine is one of three unpaired bases that mediate the specific recognition of the RNAs by the MS2 coat protein, one of ordinary skill in the art would have been motivated to place the "AAAAA" spacer sequence between the aptamer tags and the target RNA sequence to ensure correct folding and specific binding, followed by the "complete folding check" as recommended by Srisawat et al.

To summarize, the benefits and advantages of multiple (or tandem) affinity tag systems for isolating and purifying proteins for further RNA-protein interaction studies were well-known in the art as taught by Srisawat et al., Puig et al., Honey et al., and Maquat; the superior properties of aptamers compared to peptides (or antibodies) along with the availability of MS2 coat protein RNA aptamer and S1 aptamer were known in the art as taught by Srisawat et al. and Hermann et al.; the commonly known problems associated with "tagging" systems and the proper "folding" together with potential solutions were clearly suggested in the art as taught by Srisawat et al. and Puig et al.; expression vectors for TAP or MAFT systems were known to have multiple cloning sites having various restriction endonuclease sites and that identical restriction endonuclease sites (NotI) were known to flank the three consecutive peptide tag sequences in the MAFT system of Honey et al. Since all the skills and knowledge required to arrive at the claimed invention were not only known in the art but also within the technical grasp of one of ordinary skill in the art at the time of the invention, one of ordinary skill in the art would have

had an expectation of success in arriving at the claimed invention through routine optimization experimentation, and therefore, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-13, 15-17, and 20-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to an RNA fusion molecule comprising a spacer that is a sequence of 4-10 identical nucleotides, wherein the spacer sequence separates the target RNA sequence and the RNA tags, and functions to ensure proper folding of the RNA tags and to discourage interaction between the RNA tags and the target RNA sequence. As written, the claimed spacer sequence reads on "AAAA", "TTTT", "UUUU", "CCCC", "GGGG", and variants thereof. However, the specification states, "Examples of suitable insulator elements include, but are not limited to stretches of 4-5 identical nucleotides (eg, adenosines) coupled with paired restriction sites that do not interact with the tag or bait sequences." on page 15. The specification also teaches that the "stretches of identical nucleotides" can consist of 8-10 adenosine nucleotides.

See page 18. Hence, the specification provides structure/function correlation only for the polynucleotide sequence of adenosines and its function as a "suitable" spacer. That is, the specification does not adequately describe whether a polynucleotide sequence of repeated cytosines would properly function as a spacer by ensuring proper folding of RNA tags and discouraging interaction between the RNA tags and the target RNA sequence. Furthermore, the declaration filed on March 12, 2008, see page 2, explicitly states that "One skilled in the art would understand that A and U nucleotides of RNA do not hybridize as tightly as C and G nucleotides, hence the preference for A or U, vs. C or G as they will be less likely to interact strongly with the "tag" and "target" sequences, thus allowing for proper folding of the RNA fusion molecule components." Thus, in view of the declared statement, a spacer sequence of "CCCC" or "GGGG" would not function to ensure proper folding of the RNA tags and to discourage interaction between the RNA tags and the target RNA sequence, as required by the claims. Hence, the disclosure of "stretches of 4-5 identical nucleotides (eg, adenosines)" or "insulator elements, consisting of 8-10 adenosines" is not representative of the entire genus of the spacer sequences claimed in the instant case. Accordingly, one of ordinary skill in the art would agree that the inventors were not in possession of the entire genus of spacer sequence at the time of the invention.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
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